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Synthesis of aminoethanethiol trityl ether ligands for ruthenium-catalysed asymmetric transfer hydrogenation

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Abstract—A series of chiral aminoethanethiol ethers was synthesised by the regioselective and stereospecific ring opening of the (*R*)-trityl(thiiranylmethyl)ether and examined in the hydrogen transfer reduction of different aromatic ketones. High conversions (>99%) and enantioselectivities (91%) were obtained under mild reaction conditions.

1. Introduction

Chiral organometallic species acting as homogeneous asymmetric catalysts play a key role in fine and medicinal chemistry. As only one enantiomer usually exerts the desired biological activity, the stereochemical control of multi-step reactions has become imperative. In this respect, chiral-induction is nowadays one of the most efficient tools available with many industrial processes relying on this principle. Among the numerous methods for the synthesis of optically active compounds, one of the most attractive is the asymmetric hydrogenation by hydrogen transfer used principally in the preparation of chiral secondary alcohols from prochiral ketones.[1] In order to optimise this enantioselective reduction using 2-propanol, pioneering important efforts have been devoted to the design of efficient catalytic systems such as Ir,[2] Rh[3] or Ru[4] complexes, these latter appearing rapidly as the most common ones. Among the best are the Ru(II) complexes using monosulfonamides as ligands developed by Noyori[5] and Knochel,[6] bis(oxazolinylmethyl)amines obtained by Zhang[7] or thioureas synthesised by our group[8] with up to 95% ee in the reduction of various ketones. β-Amino alcohols were also described as suitable ligands for the enantioselective reduction of aromatic ketones with rather varying levels of yields and selectivities. While Noyori et al.[9] reported the use of several chiral 2-amino-1,2-diphenylethanol compounds, Wills et al.[10] obtained excellent ee values (up to 98%) with the rigid (1*S*,2*R*)-(+)-*cis*-1-amino-2-indanol. Andersson et al.[11] proposed the use of the 2-azanorbornyl-methanol, which led to similar results. More recently, Pericas et al.[12] reported the synthesis and use of enantiomerically pure β-amino alcohol ligands obtained from protected epoxy alcohols by regioselective and stereospecific ring opening of the epoxide with nitrogen nucleophiles. Surprisingly, there is no report concerning the use of β-aminothiol analogues from protected thiirane alcohols as chiral ligands in hydrogen transfer reductions. Nevertheless, it should be interesting to evaluate the activity of the thiol derivatives, known to be much more acidic than the alcohol analogues. In fact, there are only few reports on the use of aminoethanethiol derivatives in asymmetric catalysis, especially described as ligands in the asymmetric addition of diethylzinc[13] or alkyllithium[14] reagents to aldehydes. For these applications, the chiral compounds were exclusively prepared from amino acid derivatives, which required several steps. More generally, the nucleophilic opening of thiiranes with amines constitutes a well recognised route for the synthesis of aminoethanethiol derivatives.[15] Unfortunately, this reaction suffers from low to modest yields,[16] and requires either high temperatures in sealed tubes with an excess of amines or an activation by a thiophilic metal cation, such as silver nitrate.[17] Recently, Dong et al.[18] optimised the

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regioselective opening of 2,2-dimethylthiirane or 1-thiaspiro[2.5]octane suggesting an S_N2 type nucleophilic attack of the amine on the thiirane.

We report herein on how chiral β-aminoethanethiol trityl ether ligands **4a**–**e** can be efficiently prepared from the starting chiral (*R*)-trityl(thiiranylmethyl)ether following the same strategy that was generally applied to the regioselective ring opening of protected glycidol analogues. The ligands synthesised in this manner have been successfully optimised, applied to the metal-catalysed transfer hydrogenation of ketones and compared with the β-amino alcohol trityl ether ligand **5**. As has been well established in the literature,[10] the essential role of primary or secondary amine functions in the process guided our choice towards the use of this type of substituent groups.

2. Ligand synthesis

Literature precedents for the synthesis of chiral nonracemic thiiranes are rare.[19] Episulfides are most commonly synthesised from epoxides using thiourea or potassium thiocyanate.[20] On chiral epoxides, these reactions proceed with an inversion of the configuration. We synthesised chiral (*R*)-trityl(thiiranylmethyl)ether **2** by the treatment of the commercially available (*R*)-trityl glycidyl ether **1** with thiourea in methanol with a good yield of 95%. Ring opening of **2** with amine derivatives **3a**–**e** in MeOH gave the desired β-amino thiols **4a**–**e** after purification by silica gel chromatography with acceptable yields (50–70%) (Scheme 1). The opening occurred in a totally stereospecific manner exclusively at the least hindered carbon, based on a regioselective procedure using $CaCl_2$ as catalyst. Spectroscopic data were in accordance with the expected structures of the ligands while no traces of diastereoisomers were observed when using either (*R*)- or (*S*)-α-methylbenzylamine. The most notable features in the ^1H NMR spectra were the protons α to the sulfur, which were found in the range of 2.7–3.1 ppm as complex multiplets resulting from ^1H–^1H coupling. Concurrently, β-amino alcohol **5** was prepared in 72% yield by the ring opening of (*R*)-trityl glycidyl ether **1** with benzylamine in the presence of $CaCl_2$.

3. Transfer hydrogenation of aromatic ketones

Each ligand was studied under standard experimental conditions. The ruthenium (II) complexes were prepared in situ by heating a mixture of $[Ru(p\text{-cymene})Cl_2]_2$ and the chiral ligands in 2-propanol and toluene for 30 min under argon (Ru atom/aminothiol = 1:2). After the catalyst solution was cooled to room temperature, the ketone in 2-propanol was introduced (S/C = 20) and the reduction conducted in the presence of potassium *tert*-butoxide (2.5 equiv per Ru atom).

Initial studies were performed using acetophenone **6a** as a substrate with the different aminothiol ruthenium (II) complexes (Scheme 2). The results are summarised in Table 1.

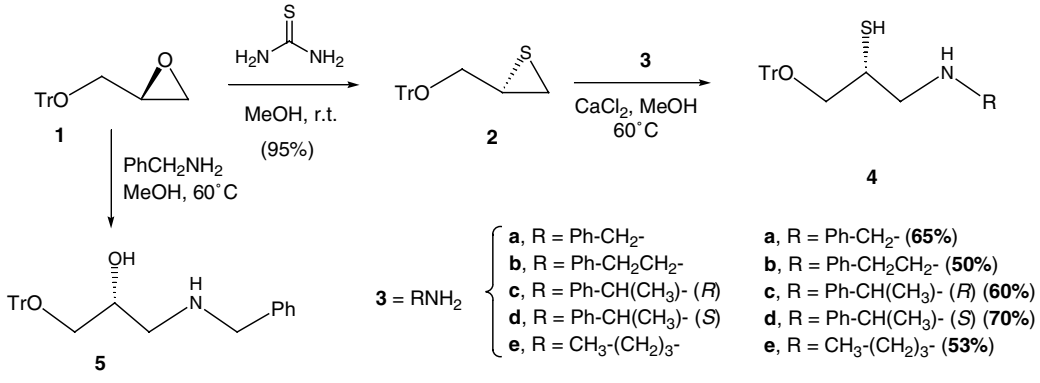
The reductions to phenylethanol achieved with Ru(II) complexes prepared in situ with chiral aminothiols **4a**–**e** were not quantitative, the highest conversion being obtained with (*S*)-**4a** ligand (86%, entry 1). With (*S*)-**4a**, -**4b** and -**4e** ligands, (*R*)-phenylethanol was obtained predominantly, with the highest asymmetric induction being 83% and 84% using (*S*)-**4a** and (*S*)-**4b**, ligand, respectively, (entries 1 and 2). However, the use of (*S*,*R*)-**4c** and (*S*,*S*)-**4d** ligands significantly decreased the enantioselectivity with low ee's (entries 3 and 4). With these ligands, the sense of asymmetric induction seemed to be determined by the configuration of the amine-bearing carbon, the (*S*,*R*)-aminothiol afforded

Table 1. Reduction of acetophenone catalysed by Ru(II)-aminothiol complexes

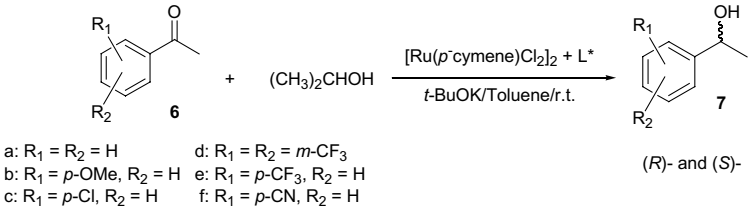
Entry	L*	Time (h)	Yield[a] (%)	Ee[a] (%)	Config.
1	(*S*)-**4a**	1	86	83	(*R*)
2	(*S*)-**4b**	1	63	84	(*R*)
3	(*S*,*R*)-**4c**	1	45	7	(*S*)
4	(*S*,*S*)-**4d**	1	35	5	(*R*)
5	(*S*)-**4e**	1	64	61	(*R*)
6	(*R*)-**5**	1	97	84	(*S*)

Conditions: reactions were carried out using a 0.03 M solution of acetophenone (0.5 mmol) in 2-propanol/toluene (2:1); ketone/Ru/ligand/*t*-BuOK = 10:1:2:2.5; room temperature.

[a] Conversion and ee were determined by GLC analysis using a chiral column (lipodex A, 25 m).



Scheme 1.



Scheme 2.

(*S*)-phenylethanol, whereas the (*S*,*S*) auxiliary gave the (*R*)-enriched alcohol. A steric hindrance effect of the methyl group could explain this result, although the spectacular decrease in both yield and selectivity indicates a very strong dependency upon this parameter.

With the amino alcohol ligand (*R*)-**5**, good yield and enantioselectivity were observed (97% and 84%, respectively, entry 6) similar to those obtained with the amino thiol ligand (*S*)-**4a** and higher than those described in literature with other amino alcohol analogues confirming the strong effect of the steric bulk of the alkoxy group, as predicted by Pericas et al.[12]

We also studied the influence of the different parameters, which govern the transfer hydrogenation of acetophenone **6a** with the (*S*)-**4a** according to the reaction time, temperature, (*S*)-**4a**/Ru ratio and catalyst precursor. As shown in Tables 2 and 3, the best conversion (91%) was reached in 1 h at room temperature with [Ru(*p*-cymene)Cl_2]$_2$ as a catalytic precursor and a L*/Ru ratio of 1.5. The best ee (87%) was obtained under the same conditions but with a lower temperature, (−10 °C, Table 2).

Table 2. Influence of the L*/Ru ratio and temperature on the reduction of acetophenone catalysed by Ru(II)-aminothiol complexes

Entry	L*/Ru	*T* (°C)	Yield (%)	Ee (%)
1	0.5	Rt	71	20 (*S*)
2	1	Rt	23	3 (*R*)
3	1.5	Rt	91	76 (*R*)
4	2	Rt	86	83 (*R*)
5	2	15	65	85 (*R*)
6	2	−10	45	87 (*R*)
7	2	−20	20	85 (*R*)
8	2.5	Rt	78	43 (*R*)

Conditions: reactions were carried out using a 0.03 M solution of acetophenone (0.5 mmol) in 2-propanol/toluene (2:1); ketone/Ru/*t*-BuOK = 10:1:2.5.

Table 3. Influence of reaction time ratio and catalytic precursor on the reduction of acetophenone

Entry	Catalyst precursor	Time (h)	Yield (%)	Ee (%)
1	[Rh(COD)Cl]$_2$	1	5	4 (*S*)
2	[Ir(COD)Cl]$_2$	1	3	16 (*R*)
3	[Ru(COD)Cl_2]$_n$	1	6	10 (*R*)
4	Ru(PPh_3)$_3Cl_2$	1	5	40 (*S*)
5	[Ru(*p*-cymene)Cl_2]$_2$	1	86	83 (*R*)
6	[Ru(*p*-cymene)Cl_2]$_2$	4	86	78 (*R*)

Conditions: reactions were carried out using a 0.03 M solution of acetophenone (0.5 mmol) in 2-propanol/toluene (2:1); ketone:M:ligand:*t*-BuOK = 10:1:2:2.5 at room temperature; L*/Ru = 2.

Generally, the catalyst precursor and the L*/Ru ratio had strong effects on both conversion (Table 2, entries 4–7) and ee (% and configuration) whereas the temperature modified only the conversion; the reaction time had a low effect both on the ee and conversion (Table 3, entry 6). However, a decrease in enantioselectivity was observed (Table 3, entry 6) after prolonged reaction times. This probably arose as a result of the known reversibility of the reaction.[9]

With a L*/Ru ratio above 1, the (*R*)-enriched phenylethanol was predominantly obtained whereas the (*S*) one was enriched (20%) when the ratio was decreased to 0.5 (Table 2). Under these conditions, several metallic species were expected in the reaction mixture (Ru^0, **4a**-Ru and (**4a**)$_2$-Ru) with a predominant L–Ru catalyst, which seems to govern the asymmetric induction. As shown in Table 3, the nature of the employed metal has influence on both activity and enantioselectivity.

When coupled with (*S*)-**4a**, [Rh(COD)Cl]$_2$ and [Ir(COD)Cl]$_2$ gave low activities and enantioselectivities (Table 3, entries 1 and 2). [Ru(COD)Cl_2] and [Ru(*p*-cymene)Cl_2]$_2$ gave 10% and 83% ee, respectively, and, in both cases, the (*R*) enantiomer was the major product. As already observed[21] in the case of hydrogenation with molecular hydrogen, it should be noted that the use of the phosphorus ruthenium precursor Ru(PPh_3)$_3Cl_2$ gave of the opposite enantiomer, (*S*)-phenylethanol, as the major product.

We found that the transfer hydrogenation under 1 h at room temperature with [Ru(*p*-cymene)Cl_2]$_2$ as precursor, S/C of 20 and L*/Ru of 2 were the best conditions for the reduction of acetophenone.

Under these conditions, we finally examined the transfer reduction of aromatic ketones **6a**–**f** using the (*S*)-**4a** ligand (Table 4) and the (*R*)-**5** ligand (Table 5). Reduction of ketones **6a**–**f** led to the corresponding alcohols in low to excellent yields (28–99%) and with moderate to high ee's (45–91%) depending on the nature of the substituents.

Thus, with a S/C ratio of 20, the reduction of *p*-methoxyacetophenone **6b**, *p*-chloroacetophenone **6c** and *m*-bisfluoromethylacetophenone **6d** resulted in the corresponding alcohols with low to moderate conversion and moderate ee's (entries 2, 4 and 5). The introduction of trifluoromethyl groups at the *para*-position (ketone **6e**) increased appreciably both the activity and the enantioselectivity (entries 7).

Table 4. Reduction of ketones **6a**–**d** catalysed by Ru(II)-aminothiol **4a**-Ru catalytic system

Entry	Ketone	Time (h)	S/C	Yield (%)[a]	Ee (%)[a]
1	**6a**	1 (44)[b]	100	3 (10)[b]	46 (12)[b]
2	**6b**	1 (140)	20	8 (54)	72 (57)
3	**6b**	0.5 (1)	100	8 (10)	0 (0)
4	**6c**	1 (72)	20	28 (94)	45 (26)
5	**6d**	1	20	>99	40
6	**6d**	1	100	>99	41
7	**6e**	1	20	>99	91
8	**6e**	1	100	>99	76
9	**6f**	1	20	>99	62
10	**6f**	1	100	>99	64

Conditions: reactions were carried out using a 0.03 M solution of ketones in 2-propanol/toluene (2:1); ketone:Ru:(*S*)-**4a**:*t*-BuOK = 10:1:2:2.5; room temperature.

[a] Conversion and ee were determined by GLC analysis using a chiral column (lipodex A, 25 m).

[b] Values in parentheses refer to results obtained after prolonged reaction time.

Table 5. Reduction of ketones **6a**–**d** catalysed by Ru(II)-amino alcohol **5**-Ru catalytic system

Entry	Ketone	Time (h)	S/C	Yield (%)[a]	Ee (%)[a]
1	**6a**	3	20	98	83
2	**6a**	1 (3)	100	83 (88)	86 (88)
3	**6b**	1	20	35	76
4	**6b**	1 (3)	100	4 (15)	76 (76)
5	**6c**	1	20	100	76
6	**6c**	1 (3)	100	41 (46)	75 (78)
7	**6d**	1	20	60	88
8	**6d**	1	100	73	85
9	**6e**	1	20	>99	83
10	**6e**	1	100	26	79
11	**6f**	1	20	>99	76
12	**6f**	1	100	26	70

Conditions: reactions were carried out using a 0.03 M solution of ketones in 2-propanol/toluene (2:1); ketone:Ru:(*R*)-**5**:*t*-BuOK = 10:1:2:2.5; room temperature. Values in parentheses refer to results obtained after prolonged reaction time.

[a] Conversion and ee were determined by GLC analysis using a chiral column (lipodex A, 25 m).

The use of an S/C ratio of 100 had no effect on the reduction of ketones **6d** and **6f** in terms of conversion and enantioselectivity (entries 6 and 10), whereas a high decrease of ee or both conversions and ee's was observed with ketones **6a**,**b** and **e** under the same conditions.

With the (*R*)-**5** amino alcohol, both activity and enantioselectivity were generally enhanced (Table 5) in the transfer hydrogenation of each ketone, comparative to the use of the (*S*)-**4a** ligand. This observation led us to believe that the higher stability of the **4a**-Ru(II) complex may be due to a stronger coordination of the ligand by the S atom than the O atom of **5**.

4. Conclusion

In summary, we have developed a new family of modular aminothiol ligands and have studied the influence of different amino moieties constituting the ligands on catalytic efficiency and enantioselectivity. This study revealed that the use of the benzylamine derivative (*S*)-**4a** gave moderate to excellent results in asymmetric transfer hydrogenation for a variety of ketones. In this way, enantioselectivities up to 85% have been reached. Studies are currently in progress to optimise the ligands at the level of the alcohol protecting group.

5. Experimental

All the organic and organometallic reagents used were pure commercial product. Isopropanol was distilled over magnesium under argon. The ketones (Aldrich and Acros) were degassed and purged under argon prior to use. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM300 (^{1}H, 300 MHz, ^{13}C, 75 MHz) in $CDCl_3$ as solvent. Polarimetric measurements were performed on a Perkin–Elmer 241 apparatus, at ambient temperature. Conversions and enantiomeric excesses were determined by GC analysis on a chiral Lipodex A (25 m) column on Shimadzu GC-14A chromatograph using a flame-ionisation detector and Shimadzu C-R6A integrator.

5.1. (*R*)-Trityl(thiiranylmethyl)ether 2

To a solution of (*R*)-glycidyl tritylether **1** (2 g; 6.3 mmol) dissolved in 300 mL of degassed MeOH, was added the thiourea (1.05 g; 13.86 mmol) and the mixture stirred at room temperature for 48 h. After evaporation of the solvent, the urea was eliminated by precipitation in dichloromethane. The crude product was purified by flash chromatography on silica gel (heptane/CH_2Cl_2: 50:50) to give a white solid of **2**. Yield 95%. Mp = 65–66 °C; $[\alpha]_D^{25} = -26.5$ (*c* 1 dichloromethane). ^{1}H NMR ($CDCl_3$): 2.15 (dd, 1H, CH_2, $J = 5.2$ Hz, $J = 1$ Hz); 2.51 (dd, 1H, CH_2, $J = 4.8$ Hz, $J = 1.3$ Hz); 3.0–3.4 (m, 2H, CH_2); 3.4–3.5 (m, 1H, CH); 7.1–7.6 (m, 15H, 3ArH). ^{13}C NMR ($CDCl_3$): 23.8 (CH_2); 33.0 (CH); 68.0 (CH_2); 86.9 (C); 127.2, 127.9, 128.7 (ArCH); 144.0 (ArC).

5.2. Ligand (*S*)-4a

(*R*)-Trityl(thiiranylmethyl)ether ether **2** (0.5 g; 1.53 mmol) was dissolved in 160 mL of degassed MeOH. Calcium chloride was then added (0.5 g; 4.59 mmol), followed by benzylamine **3a** (20 equiv). The solution was heated at 60 °C for 24 h and then stopped. The organic layer was washed with ammonium chloride (10 mL), extracted with dichloromethane (500 mL) and washed again with sodium chloride (7 mL) and water (6 mL). The resulting organic extract was dried over $MgSO_4$ and purified by chromatography (AcOEt/heptane: 30:70) to give pure (*S*)-**4a** as a yellowish oil. Yield 65%. $[\alpha]_D^{25} = -49.4$ (*c* 1 toluene). ^{1}H NMR ($CDCl_3$): 1.5–1.6 (br s, 1H, SH); 2.67 (dd, 1H, CH_2, $J = 7.3$ Hz; $J = 12$ Hz); 2.85 (dd, 1H, CH_2, $J = 6$ Hz; $J = 11$ Hz); 2.9–3.0 (m, 1H, CH); 3.1–3.3 (m, 3H, CH_2 and NH); 3.6 (d, 2H, CH_2, $^{3}J = 4$ Hz); 7.1–7.3 (m, 20H, 4ArH). ^{13}C NMR ($CDCl_3$): 49.7 (CH_2); 52.9 (CH); 53.7, 64.1 (CH_2); 87.0 (C); 127.0, 127.6, 127.9, 128.2, 128.4, 129.0 (ArCH); 140.2; 143.9 (ArC).

The same procedure was used for the synthesis of ligands (*S*)-**4b**, (*S*,*R*)-**4c**, (*S*,*S*)-**4d** and (*S*)-**4e**.

(*S*)-**4b** was obtained as a yellowish oil in 50% yield. $[\alpha]_D^{25} = +6.6$ (*c* 1 toluene) ^{1}H NMR ($CDCl_3$): 1.3–1.5 (m, 2H, CH_2); 1.5–2.0 (m, 1H, SH); 2.6–3.2 (m, 6H, $2CH_2$, NH, CH); 3.2–3.5 (m, 2H, CH_2); 7.2–7.5 (m, 20H, 5ArH). ^{13}C NMR ($CDCl_3$): 36.6, 50.2, 51.3 (CH_2); 52.9 (CH); 65.2 (CH_2); 86.8 (C); 126.2, 127.2, 127.9, 128.3, 128.5, 128.8, 129.2 (ArCH); 137.9, 143.9, 144.0 144.1 (ArC).

(*S*,*R*)-**4c** was obtained as a yellowish oil in 60% yield. $[\alpha]_D^{25} = +26.7$ (*c* 1 toluene). ^{1}H NMR ($CDCl_3$): 1.35 (d, 3H, CH_3, $J = 6.5$ Hz); 1.5–1.7 (br s, 2H, NH, SH); 2.6–2.9 (m, 2H, CH_2); 2.9–3.1 (m, 1H, CH); 3.32 (d, 2H, CH_2, $J = 5.4$ Hz); 3.6–3.8 (q, 1H, CH, $J = 6.5$ Hz); 7.2–7.5 (m, 20H, 4ArH). ^{13}C NMR ($CDCl_3$): 24.5 (CH_3); 48.2 (CH_2); 53.0, 58.2 (CH) 64.1 (CH_2); 86.9 (C); 126.7, 127.1, 127.9, 128.4, 128.5, 129.2 (ArCH); 137.9, 143.9, 144.0, 145.6 (ArC).

(*S*,*S*)-**4d** was obtained as a white solid in 70% yield. Mp = 50 °C; $[\alpha]_D^{25} = +19.75$ (*c* 0.8 toluene); ^{1}H NMR ($CDCl_3$): 1.2 (d, 3H, CH_3, $J = 6.4$ Hz); 1.4–1.6 (m, 1H, SH); 2.47 (dd, 1H, CH_2, $J = 6.9$ Hz, $J = 12.4$ Hz); 2.65 (dd, 1H, CH_2, $J = 5.3$ Hz; $J = 12.4$ Hz); 2.7–2.8 (m, 1H, CH); 3.0–3.2 (m, 3H, CH_2 and NH); 3.5–3.6 (m, 1H, CH); 7.1–7.3 (m, 20H, 4ArH). ^{13}C NMR ($CDCl_3$): 24.4 (CH_3); 47.9 (CH_2); 52.9, 57.9 (CH); 64.1 (CH_2); 86.8 (C); 126.6, 126.9, 127.1, 127.8, 128.3, 128.8 (ArCH); 143.8; 143.9; 144.0, 145.5 (ArC).

(*S*)-**4e** was obtained as a yellowish oil in 53% yield. $[\alpha]_D^{25} = -7.4$ (*c* 0.5 toluene). ^{1}H NMR ($CDCl_3$): 0.7–0.8 (t, 3H, CH, $J = 7.7$ Hz); 1.1–1.2 (m, 4H, $2CH_2$); 2.3–2.6 (m, 3H, CH_2 and SH); 2.7 (d, 2H, CH_2, $J = 7.4$ Hz); 2.7–2.8 (m, 1H, NH); 3.0–3.1 (m, 1H, CH); 3.0–3.2 (m, 3H, CH_2 and CH); 7.0–7.2 (m, 15H, 3ArH). ^{13}C NMR ($CDCl_3$): 14.6 (CH_3); 20.9, 32.8 (CH_2); 47.9 (CH); 49.9, 51.8, 65.7 (CH_2); 87.2 (C); 127.5; 128.3; 129.2 (ArCH); 144.4 (ArC).

(*R*)-**5**: (*R*)-Glycidyl tritylether **1** (0.3 g; 0.95 mmol) was dissolved in MeOH (100) mL. Calcium chloride was then added (0.31 g; 2.84 mmol) followed by benzylamine **3a** (2.07 mL, 1.9 mmol). The solution was heated at 60 °C for 48 h and then stopped. After cooling, the organic layer was washed with ammonium chloride (10 mL), extracted with dichloromethane (350 mL) and washed by sodium chloride (5 mL) and water (6 mL). The resulting organic extract was dried over $MgSO_4$ and purified by chromatography (AcOEt/heptane: 30:70) to give pure (*R*)-**5** (0.288 g). Yield 72%. $[\alpha]_D^{25} = +30.5$ (*c* = 0.36, toluene). ^{1}H NMR ($CDCl_3$): 2.24 (br s, 2H, OH and NH); 2.62 (dd, $J = 12.1$ Hz, $J = 7.5$ Hz, CH); 2.71 (dd, $J = 12.1$ Hz, 4 Hz, CH); 3.07 (d, $J = 5.1$ Hz, 2H, CH_2); 3.66–3.77 (AB, $J = 13.2$ Hz, 2H, NCH_2); 3.8–3.9 (m, CH); 7.15–7.33 (m, 20ArH). ^{13}C NMR ($CDCl_3$): 51.3, 53.3, 66.1 (CH_2); 68.6 (CH); 86.7 (C), 127.1, 127.6, 127.9, 128.3, 128.5, 128.7, 129.1 (ArCH); 140.0, 143.8 (ArC).

5.3. General procedure for transfer hydrogenation of ketones

An appropriate amount of ligand was added to an appropriate amount of the catalyst precursor in 2 mL of 2-propanol and stirred at 80 °C for 30 min under argon. After cooling to room temperature, a solution of ketone (S/C of 20 or 100) and potassium *tert*-butoxide (2.5 equiv per metal atom) in 4 mL of 2-propanol/toluene (2:1) was added. The reduction was conducted at room temperature for the time indicated (monitored by GC). The resulting solution was neutralised with 1 M HCl and concentrated in vacuo. The residue was diluted with dichloromethane and the organic solution washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The conversion and enantiomeric excess was determined from the crude mixture by GC analysis.

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